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Original article

Outcomes of children born to mothers with systemic lupus erythematosus exposed to hydroxychloroquine or azathioprine

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Abstract

Objectives. HCQ and AZA are used to control disease activity and reduce risk of flare during pregnancy in patients with SLE. The aim of this study was to determine the outcomes of children born to mothers with SLE exposed to HCQ or AZA during pregnancy and breast-feeding.

Methods. Women attending UK specialist lupus clinics with children ≤17 years old, born after SLE diagnosis, were recruited to this retrospective study. Data were collected using questionnaires and from clinical record review. Factors associated with the outcomes of low birth weight and childhood infection were determined using multivariable mixed-effects logistic regression models.

Results. We analysed 284 live births of 199 mothers from 10 UK centres. The first pregnancies of 73.9% of mothers (147/199) were captured in the study; (60.4%) (150/248) and 31.1% (87/280) children were exposed to HCQ and AZA, respectively. There were no significant differences in the frequency of congenital malformations or intrauterine growth restriction between children exposed or not to HCQ or AZA. AZA use was increased in women with a history of hypertension or renal disease. Although AZA was associated with low birth weight in univariate models, there was no significant association in multivariable models. In adjusted models, exposure to AZA was associated with increased reports of childhood infection requiring hospital management [odds ratio 2.283 (1.003, 5.198), P = 0.049].

Conclusions. There were no significant negative outcomes in children exposed to HCQ in pregnancy. AZA use was associated with increased reporting of childhood infection, which warrants further study.

Key words: HCQ, AZA, SLE, pregnancy, adverse outcomes

Rheumatology key messages

- Hydroxychloroquine exposure in pregnancy and breastfeeding is not associated with any adverse outcomes.
- Low birth weight is associated with pre-eclampsia but not azathioprine or hydroxychloroquine use.
- Children born to mothers requiring azathioprine in pregnancy or breastfeeding need careful follow-up.

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CLINICAL SCIENCE

Introduction

Immunosuppressive agents are commonly used in SLE during pregnancy, to ensure the optimum outcome for both mother and child. It is essential to ensure optimal disease control prior to and during pregnancy, as active SLE has been demonstrated to be associated with adverse maternal and foetal outcomes, including fewer live births, earlier deliveries, and small-for-gestational-age babies [1, 2]. Continuing effective medication is also important because of the increased risk of lupus flare during pregnancy or in the early post-partum period [3].

HCQ is an important drug in the management of SLE and reduces the risk of lupus flare. Women with SLE who continue HCQ throughout pregnancy have lower disease activity and lower prednisolone doses at the end of pregnancy than those who stop [4, 5]. In anti-Ro/SSA antibody–positive mothers with history of a child with congenital heart block (CHB), HCQ reduces the risk of subsequent CHB by over 50% [6]. In systematic reviews, HCQ is not associated with any increased risk of prematurity, spontaneous abortion or foetal death [7] or retinal toxicity, although early electroretinogram changes, of uncertain significance, have been reported in very small numbers of children [8].

AZA, the pro-drug of 6-mercaptopurine (6-MP), is used to treat several conditions, including SLE. AZA use (at <2 mg/kg body weight) is considered compatible with pregnancy [9], and switching from MMF to AZA prior to pregnancy is not associated with a risk of renal flare [10].

Although HCQ, AZA and glucocorticoids are considered to be compatible with pregnancy and breastfeeding [9], there are little data regarding the longer-term outcomes of children exposed to HCQ and AZA [11, 12]. The aim of this study was to determine outcomes in children up to the age of 17 exposed to HCQ or AZA in utero or during breastfeeding by mothers with SLE.

Methods

Participants were recruited from 10 hospital sites within the UK [Birmingham (3 sites), London (2 sites), Bath, Manchester, Blackburn, Sheffield and Southampton]. Women who had $\geq$4 1997 Updated ACR Classification Criteria for SLE [13] prior to pregnancy and who regularly attended a rheumatology outpatient department were identified.

Retrospective data were collected using a previously piloted questionnaire, between 2007 and 2011 (see Supplementary Data S1–2, available at Rheumatology online). The first part of the questionnaire was completed by women and by collection of maternal data via interview and reviewing the medical records. Maternal data collected included: ACR Classification Criteria for SLE, lupus-related autoantibodies, and renal biopsy results. A history of APS was defined as per the 1999 preliminary Sapporo criteria [14], although did not differentiate between thrombotic and obstetric APS. Pregnancy data collected included drug exposure at conception, during pregnancy, and during breastfeeding, and the outcome in terms of miscarriages, stillbirth, live birth, pre-eclampsia, premature delivery, intrauterine growth restriction (IUGR), birth weight and gestational age.

A second part of the questionnaire was completed by the mother to collect data on outcomes in each child up to the age of 17, including neonatal lupus rash, CHB, any other congenital malformations (using the EUROCAT definition) [15], any admissions to hospital and the diagnosis, including infections, outpatient visits and the reasons for the visits, and any evidence for developmental problems, including developmental delay (DD), special educational needs and attention deficit disorder (ADD). Due to regional variations in management of childhood infections, those requiring hospital management (either as an inpatient, outpatient or day case) were combined for analysis.

The a priori hypothesis was that exposure to HCQ or AZA during pregnancy or breastfeeding was not associated with an increased risk of congenital abnormalities, serious childhood infection, or developmental abnormalities.

The study was approved and conducted in compliance with regulations of relevant ethics committees [North West Research Ethics Committee (07/MRE08/54) and hospital research and development departments], and all mothers provided written informed consent in accordance with the Declaration of Helsinki. If a child was over the age of 12 at recruitment, then assent was given by a parent, as approved by the ethics committee.

Statistical analysis

For descriptive analyses, frequencies were compared using non-parametric tests (Mann–Whitney U test or Chi^2 test as appropriate). Only live-born children were included. As HCQ or AZA were continued throughout pregnancy and breastfeeding in almost all cases, exposure was combined into a single variable for each drug.

As some mothers contributed more than one child to the study, univariate mixed-effects logistic regression models, with a random intercept for the mother, were used. In multivariable models, variables identified in univariate analyses and those considered to be likely confounding variables were used. Prednisolone use (yes/no) was forcibly retained in the multivariable models.

It was assumed that data regarding maternal history of LN requiring renal biopsy and hypertension were missing at random. Therefore, multiple imputation using chained equations (MICE) was conducted for these variables with 10 imputations: hypertension, renal disease, AZA use, and white ethnicity were used for MICE in the infection model, and hypertension, renal disease, AZA use, IUGR, pre-eclampsia for the low-birth-weight model. Imputed data were then used in the multivariable mixed-effects logistic regression models described above. All analyses were conducted using STATA v.16.0 (StatCorp LLC).

Results

Data were analysed for 199 women with 283 pregnancies and 284 live born children (one twin pregnancy) with

delivery dates between 1991 and 2011. Ten centres contributed data (3–134 children per centre). There was a small amount of missing data, although this was <10% for the majority of variables. The study captured 1–4 pregnancies per patient, of which 147 (73.9%) were first-ever pregnancies. The majority of patients (127/199, 63.8%) were white, 29 (14.6%) were of South Asian background and 22 (11.1%) were of Black African or Caribbean background. Hypertension predating pregnancy was present in 27/192 (14.1%) of mothers, and 42/175 (24.0%) had a previous renal biopsy; 20/199 (11.1%) of mothers had concomitant APS. The median [interquartile range (IQR)] disease duration at the time of pregnancy was 6 (3, 10) years. The demographic data of the mothers and their pregnancies are shown in Table 1, and the ACR criteria of the mothers are shown in Supplementary Table S1, available at Rheumatology online.

Maternal exposure to medications (HCQ and AZA)

Prednisolone and HCQ were commonly prescribed during pregnancy (167/283, 59.1% and 149/283, 52.7%, respectively). AZA was used in 86/283 (30.4%) pregnancies. In 38/283 pregnancies, all 3 medications were prescribed. In the majority of pregnancies (199/282, 70.8%), aspirin was prescribed, and aspirin use was more common in mothers also taking AZA or prednisolone (Table 2). Although the dose of aspirin was not collected, common practice at the time of the study was to use 75 mg daily. Low-molecular-weight heparin (LMWH) was used in 68/280 (24.0%) of pregnancies, of which 17 (27.9%) were in mothers with pre-existing APS. In mothers without pre-existing APS who were treated with LMWH, 17/51 (33.3%) mothers did not have a positive ACL antibody or LA.

There were no significant differences in the characteristics of mothers who received HCQ compared with those who did not. However, mothers receiving AZA were more likely to have a history of hypertension (31.1% vs 6.6%, $P < 0.001$) or a renal biopsy prior to pregnancy (52.1% vs 13.4% $P = 0.007$), proteinuria (32.4% vs 18.5%, $P = 0.014$), a longer duration of disease [median (IQR)] [7.5 (5, 11) vs 5 (2, 10) years, $P = 0.003$], a previous positive anti-RNP antibody (39.3% vs 20.4%, $P = 0.007$) and to be taking aspirin during the pregnancy (81.2% vs 66.3%, $P = 0.012$) (see Table 2). Of the 66 patients with proteinuria, 16 (24.2%) had pre-eclampsia.

Pregnancy outcomes and exposure to HCQ or AZA

Of 284 children (from 283 pregnancies), 149/284 (52.5%) were exposed to HCQ and 87/284 (30.6%) were exposed to AZA. The median gestational age was 38 (37, 39) weeks. Of 103/279 (36.9%) of births <38 weeks, 12/99 (12.1%) were induced due to pre-eclampsia and 15/94 (16.0%) were induced due to IUGR. In induced pregnancies, the median gestational age was 36 (32, 38) weeks. The median birth weight was 2.96 (2.49, 3.31) kg and 70/276 (25.4%) babies were <2.5 kg. Of the babies with low birth weight, 22/70 (31.4%) were reported to have IUGR.

Congenital abnormality (as defined by EUROCAT CA) occurred in 6 (2.1%) pregnancies. All 6 cases of neonatal lupus rash occurred in pregnancies with concomitant positive anti-Ro/SSA and/or La/SSB antibodies [rate of 6/111 (5.4%) in Ro/SSA/La/SSB-positive mothers, 6/284 (2.1%) overall]. Of the 7 children with CHB [overall 7/284 (2.46%)], one was born to a mother without positive anti-Ro/SSA or La/SSB antibodies. Of these 7 children, 4 had been exposed to HCQ and 3 not (including the 1 child whose mother did not have Ro/SSA/La antibodies).

Table 1 Characteristics of the mothers and their pregnancies in the cohort

Mothers in the cohort (*n* = 199)	
Age at delivery of first child in study (years) (n = 194)	31 (28, 35)
Ethnic background	
African or Caribbean	22 (11.1%)
South Asian	29 (14.6%)
White	127 (63.8%)
Chinese	4 (2.0%)
Other/Mixed	11 (5.5%)
Unknown	6 (3.0%)
Number of pregnancies per patient captured in this study	
1	127 (63.8%)
2	60 (30.2%)
3	11 (5.53%)
4	1 (0.5%)
Number of first pregnancies in this study	147 (73.9%)
Anti-dsDNA ever present (n = 191)	121 (63.4%)
Anti-Sm ever present	27 (14.4%)
Anti-RNP ever present	49 (25.7%)
Previous renal biopsy (n = 175)	42 (24.0%)
Hypertension prior to pregnancy (n = 192)	27 (14.1%)
Diagnosis of APS (n = 181)	20 (11.1%)
Pregnancies (*n* = 283)[a]	
Disease duration at time of pregnancy (years)	6 (3, 10)
Autoantibodies	
Anti-Ro/SSA (n = 263)	108 (41.1%)
Anti-La/SSB (n = 261)	55 (21.1%)
Anti-Ro/SSA or anti-La/SSB (n = 261)	111 (42.5%)
APS serology	
aCL (n = 250)	67 (26.8%)
LA (n = 258)	92 (35.8%)
Positive LA or aCL (n = 248)	121 (48.8%)
Proteinuria during pregnancy (n = 250)	67 (36.6%)
Medication use during pregnancy (*n* = 283)	
Prednisolone exposure during pregnancy	167 (59.1%)
HCQ exposure during pregnancy	149 (52.7%)
AZA exposure during pregnancy	86 (30.4%)
Prednisolone + HCQ	58 (20.5%)
Prednisolone + AZA	0
HCQ + AZA	43 (15.2%)
Prednisolone + HCQ + AZA	38 (13.4%)
Prednisolone alone	34 (12.0%)
Aspirin (n = 282)	199 (70.8%)
Low-molecular-weight heparin (n = 280)	68 (24.0%)

[a]283 pregnancies with 284 live births due to 1 set of twins.

Table 2 Characteristics of mothers and their pregnancies according to exposure to AZA or HCQ

Mothers (n = 199)	All mothers	HCQ			AZA			Prednisolone		
		Exposed (n = 107)	Not exposed (n = 92)	P	Exposed (n = 59)	Not exposed (n = 140)	P	Exposed (n = 118)	Not exposed (n = 81)	P
Ethnic background (White)	127 (63.8%)	73 (68.2%)	54 (58.7%)	0.163	36 (61.0%)	91 (65.0%)	0.593	71/118 (60.2%)	56/81 (69.1%)	0.916
Anti-dsDNA ever	121/187 964.7%)	63/97 (64.6%)	58/90 (64.4%)	0.943	41/55 (74.6%)	80/132 (60.6%)	0.069	**79/110 (71.8%)**	**42/77 (54.6%)**	**0.015**
Anti-Smith ever	27/184 (14.7%)	13/97 (13.4%)	14/87 (16.1%)	0.607	9/55 (16.4%)	18/129 (4.0%)	0.672	21/112 (18.8%)	6/72 (8.3%)	0.051
Anti-RNP ever	49/188 (26.1%)	24/100 (24.0%)	25/88 (28.4%)	0.492	**22/56 (39.3%)**	**27/20 (20.4%)**	**0.007**	35/113 (31.0%)	14/74 (18.7%)	0.600
Previous renal biopsy	42/175 (24.0%)	21/99 (21.1%)	21/76 (27.6%)	0.324	**25/48 (52.1%)**	**17/127 (13.4%)**	**<0.001**	**32/102 (21.4%)**	**10/73 (13.7%)**	**0.007**
Hypertension prior to pregnancy	27/192 (14.1%)	10/103 (9.7%)	17/89 (19.1%)	0.062	**18/56 (32.1%)**	**9/136 (6.6%)**	**<0.001**	**22/113 (19.5%)**	**5/79 (6.3%)**	**0.010**
Diagnosis of APS	20/181 (11.1%)	10 (10.1%)	10/82 (12.2%)	0.655	4/53 (7.6%)	16/128 (12.5%)	0.333	12/106 (11.3%)	8/75 (10.7%)	0.890

Pregnancies (n = 283)	All pregnancies	Exposed (n = 150)	Not exposed (n = 134)	P	Exposed (n = 86)	Not exposed (n = 198)	P	Exposed (n = 167)	Not exposed (n = 116)	P
Age at delivery (years)	32 (28, 35)	32 (29, 35)	31 (28, 35)	0.172	32 (29, 35)	32 (28, 35)	0.544	32 (29, 35)	32 (28, 35)	0.445
Disease duration (years)	6 (3, 10)	6 (3, 10)	7 (3, 11)	0.126	**7.5 (5, 11)**	**5 (2, 10)**	**0.003**	6 (3, 10)	5.5 (3, 10)	0.325
Anti-Ro/SSA	108/262 (41.1%)	53/141 (37.6%)	55/121 (45.5%)	0.197	36/77 (46.8%)	72/185 (38.9%)	0.241	68/153 (44.4%)	40/109 (36.7%)	0.209
Anti-La/SSB	55/260 (21.2%)	23/139 (16.6%)	32/121 (26.5%)	0.051	22/77 (28.6%)	33/183 (18.0%)	0.057	36/153 (23.5%)	19.107 (17.8%)	0.262
Anti-Ro/SSA or anti-La/SSB	111/260 (42.7%)	54/139 (38.9%)	57/121 (47.1%)	0.179	37/77 (48.1%)	74/183 (40.4%)	0.243	70/153 (45.8%)	41/107 (38.3%)	0.233
aCL	67/249 (26.8%)	33/131 (25.2%)	34/118 (28.8%)	0.520	25/72 (34.7%)	42/177 (23.7%)	0.076	40/144 (27.8%)	27/105 (25.7%)	0.717
LA	92/257 (35.8%)	52/136 (38.2%)	40/121 (33.1%)	0.387	30/73 (41.1%)	62/184 (33.7%)	0.264	58/149 (38.9%)	34/108 (31.5%)	0.219
Aspirin	199/281 (70.8%)	111/149 (74.5%)	88/132 (66.7%)	0.150	**69/85 (81.2%)**	**130/196 (66.3%)**	**0.012**	**133/165 (80.6%)**	**66/116 (59.9%)**	**<0.001**
LMWH	68/280 (24.6%)	41/148 (27.7%)	27/132 (20.4%)	0.158	27/85 (31.8%)	41/195 (21.0%)	0.054	45/165 (27.2%)	23/115 (20.0%)	0.163
Proteinuria	66/248 (26.8%)	35/132 (25.8%)	32/116 (27.6%)	0.745	26/75 (34.7%)	40/173 (23.1%)	0.059	**47/145 (32.4%)**	**19/103 (18.5%)**	**0.014**

Comparisons made using Chi^2 tests or Mann–Whitney U tests as appropriate. Each drug was considered independently. Bold text indicates statistically significant results. LMWH: low-molecular-weight heparin. $P < 0.05$ was considered statistically significant.

The median follow-up of children was 3.23 (1.14, 6.88) years. The follow-up duration was shorter in children exposed to HCQ [2.21 (0.58, 4.74) vs 4.55 (2.04, 9.34) years, $P < 0.001$], but there was no difference between children exposed or not to AZA. There were 99 infections requiring hospital management (either as an inpatient or outpatient) in 48/284 (16.9%) children. Among children with reported infection, the median (IQR) number of infections was 2 (1, 3). 17/284 (6.0%) had one or more of DD, ADD, special needs or a requirement for special schooling. Reported infections are described in more detail below.

There were significant differences between outcomes in pregnancies in which AZA was used and those in which it was not (Table 2). Children exposed to AZA were delivered at an earlier gestational age [37 (35, 38) vs 38 (37, 40) weeks, $P < 0.001$] and were more likely to be premature (<38 weeks gestation) [44/86 (51.2%) vs 59/193 (30.6%), $P = 0.001$]. Similarly, babies were more likely to be smaller in birth weight. There was also a greater number of children with childhood infection in those exposed to AZA [21/87 (24.1%) vs 27/197 (13.7%), $P = 0.031$). There were no differences in the reported frequency of pre-eclampsia, IUGR (or induction for either of pre-eclampsia or IUGR), CHB or other congenital abnormality (Table 3). Fewer children were reported to have special needs in the group exposed to HCQ [1/148 (0.7%) vs 6/135 (4.4%), $P = 0.041$], but this was not significant when combined with DD and ADD [6/149 (4.0%) vs 11/135 (8.2%), $P = 0.144$].

Maternal and pregnancy factors associated with low birth weight

As low birth weight (<2.5 kg) was more common in children exposed to AZA, a two-level mixed-effects logistic regression model, with the mother as the random intercept, was used. In univariate analyses, exposure to AZA, aspirin and LMWH, and pre-eclampsia were all associated with low birth weight. There was no association with APS, aCL or LA. In multivariable models using the variables above, only pre-eclampsia [OR 4.2 (1.07, 16.65), $P = 0.040$] was independently associated with low birth weight (Table 4). Given that birth weight is reported to increase with subsequent pregnancies, in a sensitivity analysis, the number of pregnancies was included in the multivariable model. In this sensitivity analysis, only pre-eclampsia [OR 5.11 (1.62, 16.19) $P = 0.005$] was associated with low birth weight, as before. These findings were also observed in a model in which maternal history of hypertension and renal biopsy were imputed (Table 4).

Maternal and pregnancy-related risk factors for childhood infection

Infections requiring hospital management were reported in 48/284 (16.9%) children during the follow-up period. To avoid bias from recurrent infections in some children, we analysed risk factors based on the first recorded infection; the most frequent were pneumonia (10/48, 20.8%), bronchiolitis (7/48, 14.6%) and pharyngitis/tonsillitis (4/48, 8.4%) (Table 5).

In univariate analyses, both AZA use and mother being of white background were significantly associated with childhood infection. Duration of follow-up and prednisolone use was forcibly retained in the multivariable models. In both the multivariable model (including gestational age and birth weight) and the imputed model (also including maternal history of hypertension and renal disease), white background and AZA exposure remained statistically significant (Table 6). In a sensitivity analysis of first-ever pregnancies (146 women), exposure to AZA remained associated with childhood infection in both univariate [OR 3.21 (1.34, 7.66) $P = 0.009$] and multivariable models [OR 2.72 (1.67, 3.64) $P = 0.02$] using the same covariates above. In children with infection, there was no difference in the number of reported infections per child in those exposed to AZA compared with those who were not [2 (1, 2) vs 2 (1, 4), $P = 0.997$].

Discussion

This is one of the largest studies examining outcomes in children born to mothers with SLE beyond the early post-natal period. Children were included up to the age of 17 years, capturing events both in early and late childhood.

The study focused on associations between HCQ and AZA exposure during pregnancy and low birth weight and childhood infection. Other outcomes, including pre-eclampsia, IUGR, congenital malformation, neonatal lupus rash and CHB, were infrequent in our study and did not differ in frequency between groups exposed to HCQ or AZA. The rates of CHB or other congenital abnormalities in this study were 2.5% and 2.1%, respectively. The prevalence of CHB was similar to that previously reported [16], but greater than the 1/154 observed in anti-Ro/SSA–positive mothers in the PROMISSE study [17]. Our study did not include data from prior pregnancies, which may influence the risk of CHB (i.e. up to 20% if a previous child had CHB), although the first pregnancy was captured in nearly 75% of mothers. The lower rates of CHB in the PROMISSE study may also be due to increased HCQ use (64.7% compared with 52.7% in our study).

HCQ is recommended for all women with SLE during pregnancy [18, 19]; it reduces the risk of CHB [6] and may reduce the incidence of pre-eclampsia, although data are conflicting [20]. In our study, there was no increased pre-term birth, IUGR or congenital abnormality in children exposed to HCQ. Of note, the number of patients taking HCQ was relatively modest, reflecting clinical practice at the time of the study. Although there was no difference in the frequency of CHB in children exposed to HCQ, the total number of children with CHB was small. A number of studies have confirmed the safety of HCQ in pregnancy. A meta-analysis including studies up to 2014 inclusive (7 cohort studies and 1

Table 3 Pregnancy outcomes according to exposure to AZA or HCQ in all pregnancies/children (univariate analysis)

	All children (*n* = 284)	HCQ			AZA		
		Exposed (*n* = 149)	Not exposed (*n* = 135)	*P*	Exposed (*n* = 87)	Not exposed (*n* = 197)	*P*
Characteristics of children							
Age of child at time of study (years) (n = 284)	3.23 (1.14, 6.88)	**2.21 (0.58, 4.74)**	**4.55 (2.04, 9.34)**	**<0.001**	3.28 (1.14, 8.31)	3.11 (1.08, 6.35)	0.682
Gestational age at delivery (weeks) (*n* = 280)	38 (37, 39)	38 (37, 39)	38 (37, 39)	0.416	**37 (35, 38)**	**38 (37, 40)**	**<0.001**
Pre-term delivery at <38 weeks (*n* = 280)	103/279 (36.9%)	58/148 (39.2%)	45/131 (34.4%)	0.403	**44/86 (51.2%)**	**59/193 (30.6%)**	**0.001**
Delivery method (n = 281)							
Vaginal	139 (49.6%)	71 (49.0%)	68 (50.4%)		48 (55.8%)	91 (47.2%)	
Assisted	30 (10.7%)	16 (11.0%)	14 (10.4%)	0.967	5 (5.8%)	25 (12.8%)	0.151
Caesarean section	111 (39.5%)	58 (39.7%)	53 (39.3%)		33 (38.4%)	78 (40.0%)	
Birth weight (kg) (*n* = 277)	2.96 (2.49, 3.31)	2.92 (2.49, 3.31)	3.00 (2.50, 3.34)	0.915	**2.77 (2.32, 3.28)**	**3.00 (2.57, 3.34)**	**0.018**
Low birth weight (<2.5 kg) (*n* = 277)	70/276 (25.4%)	39/146 (26.7%)	31/130 (23.9%)	0.585	**29/83 (34.9%)**	**41/193 (21.2%)**	**0.016**
Adverse outcomes during pregnancy reported by mothers							
Pre-eclampsia	328/267 (10.5%)	15/142 (10.6%)	13/125 (10.4%)	0.982	11/82 (13.4%)	17/185 (9.2%)	0.299
Pre-eclampsia requiring induction (n = 269)	19/268 (7.1%)	13/143 (9.1%)	6/125 (4.8%)	0.172	7/82 (8.5%)	12/186 (6.5%)	0.532
IUGR (n = 268)	31/267 (11.6%)	16/140 (11.4%)	15/127 (11.8%)	0.906	10/82 (12.2%)	21/185 (11.4%)	0.843
IUGR requiring induction	19/267 (7.1%)	10/140 (7.1%)	9/127 (7.1%)	0.986	7/82 (8.5%)	12/186 (6.4%)	0.540
Induction (either PET or IUGR)	32/283 (11.3%)	19/149 (12.8%)	13/134 (9.7%)	0.419	12/86 (13.8%)	20/197 (10.2%)	0.353
Neonatal outcomes reported by mothers							
Neonatal lupus rash (all children)	6/284 (2.1%)	4/149 (2.7%)	2/135 (1.5%)	0.481	2/87 (2.3%)	4/197 (2.0%)	0.885
Congenital Heart Block (CHB)	7/284 (2.5%)	4/149 (2.7%)	3/135 (2.2%)	0.802	2/87 (2.3%)	5/197 (2.5%)	0.905
Congenital abnormality (EUROCAT CA)	6/284 (2.1%)	4/149 (2.7%)	2/135 (1.5%)	0.486	2/87 (2.3%)	4/197 (2.0%)	0.885
Infection	48/284 (16.9%)	24/149 (16.1%)	24/139 (17.8%)	0.708	**21/87 (24.1%)**	**27/197 (13.7%)**	**0.031**
Developmental delay, attention deficit disorder, special schooling or special needs	17/284 (6.0%)	6/149 (4.0%)	11/135 (8.2%)	0.144	6/87 (6.9%)	11/197 (5.6%)	0.667
Developmental delay	14/283 (5.0%)	6/148 (4.1%)	8/135 (5.9%)	0.679	5/87 (5.8%)	9/196 (4.6%)	0.679

(continued)

Table 3 Continued

	All children ($n = 284$)	HCQ			AZA		
		Exposed ($n = 149$)	Not exposed ($n = 135$)	*P*	Exposed ($n = 87$)	Not exposed ($n = 197$)	*P*
Attention deficit disorder	3/283 (1.1%)	0	3/135 (2.2%)	0.068	0	3/196 (1.5%)	0.246
Special schooling	6/283 (2.1%)	1/148 (0.7%)	5/135 (3.7%)	0.077	2/87 (2.3%)	4/196 (2.0%)	0.0.889
Special needs	**7/283 (2.5%)**	**1/148 (0.7%)**	**6/135 (4.4%)**	**0.041**	3/87 (3.4%)	4/196 (2.0%)	0.482

Data are n (%) or median (IQR) as appropriate. Comparisons made using the Chi^2 test for categorical variables or the Mann–Whitney U test for continuous variables. Bold text indicates statistically significant results. IUGR: intrauterine growth restriction. $P < 0.05$ was considered statistically significant.

RCT) compared outcomes between 800 HCQ-exposed and 1130 control pregnancies and confirmed no increased risk of low birth weight or congenital abnormalities with HCQ exposure [21]. A subsequent large cohort study of patients with a spectrum of autoimmune diseases also supports the safety of HCQ [22]. In contrast, a population-based cohort study by Huybrechts et al. (2021) reported an increased risk congenital malformation babies exposed to HCQ during the first trimester [adjusted relative risk (RR) 1.26 (1.04, 1.54)]. Importantly, the mean (S.D.) daily dose of HCQ was high 371 (379) mg, and the increased risk only occurred in mothers receiving $\geq$400 mg/day [23]. Although the dose was not recorded in our study, the authors are not aware of any woman receiving a dose of $>$400 mg/day.

There was no increased risk of childhood infection or developmental problems with HCQ exposure. There was a small reduction in the number of children with special needs, but the number of children was small and the follow-up durations shorter in children exposed to HCQ; therefore, this observation should be interpreted with caution. A Danish study examined school performance in children and reported no statistically significant difference between children exposed to HCQ and/or other immunosuppressants with those who were not. In this large population-based study (including 312 children of mothers with SLE), SLE diagnosis and medication exposure were identified using ICD-10 codes and prescriptions collected during pregnancy [24]. In contrast, in our study all women fulfilled classification criteria for SLE and confirmed that they were taking the medication as prescribed. Although a smaller study of 40 patients of children born to mothers with SLE and/or APS used different outcome measures, the frequency of cognitive impairment was 7%, similar to the 6% observed using our combined measure [25].

Fewer studies have investigated the safety of AZA in pregnancy. We did not find any association between AZA use and pre-eclampsia or IUGR. Associations between AZA and low birth weight and preterm birth were only observed in univariate analyses and not in multivariable models. As might be expected, mothers receiving AZA were more likely to have a history of renal disease or hypertension and were therefore included our models. Our findings are comparable with those of previous studies, demonstrating no adverse early post-partum outcomes in patients with SLE [26] or inflammatory bowel disease (IBD) receiving AZA [27, 28]. Earlier studies in IBD suggested an increased risk of congenital abnormalities, but confounding effects of active disease or concomitant medication are likely to be important [29].

A smaller retrospective study by Marder et al. (2013) reported that AZA exposure was associated with increased special educational service use, especially in children over 2 years of age [30]. Our study, in which approximately one-third of children had reached school age, did not find such an association and supports findings of a smaller study in children of mothers with IBD [31] and a study of 92 children of mothers with SLE,

Table 4 Mixed-effects logistic regression model of low birth weight in all pregnancies (n = 283)

	Univariate model			Multivariable model (only variables included in the model are shown)			Imputed multivariable model[a]		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Fixed maternal factors									
Ethnic background (White)	0.886	0.387, 2.030	0.776						
History of hypertension	2.569	0.847, 7.796	0.096				1.142	0.739, 4.526	0.192
History of renal disease	1.933	0.691, 5.411	0.209				0.709	0.198, 2.544	0.593
APS[b]	1.877	0.486, 7.253	0.361						
LA	1.452	0.590, 3.569	0.417						
aCL	1.749	0.613, 4.986	0.295						
dsDNA (ever)	1.516	0.614, 3.745	0.367						
Sm (ever)	1.806	0.542, 6.023	0.336						
RNP (ever)	0.956	0.373, 2.450	0.925						
Pregnancy factors									
Maternal age at delivery	1.012	0.936, 1.091	0.785						
Maternal disease duration	0.969	0.892, 1.051	0.444						
Pregnancy number	0.870	0.609, 1.242	0.444						
Pre-eclampsia	**6.315**	**1.882, 21.195**	**0.003**	**5.262**	**1.654, 16.747**	**0.005**	**5.829**	**1.835, 18.519**	**0.003**
Proteinuria	1.503	0.601, 3.763	0.384						
HCQ	1.237	0.576, 2.656	0.585						
AZA	**2.554**	**1.085, 6.012**	**0.032**	1.749	0.715, 4.279	0.221	1.829	0.739, 4.526	0.192
Prednisolone	1.833	0.849, 3.959	0.123	1.228	0.524, 2.878	0.637	1.269	0.583, 2.759	0.548
Aspirin	**2.485**	**1.050, 6.183**	**0.039**	2.072	0.715, 4.279	0.160	1.666	0.702, 3.954	0.247
LMWH	**2.264**	**1.019, 5.030**	**0.045**	1.899	0.806, 4.475	0.143	1.845	0.833, 4.090	0.131
Ro/SSA (current)	1.240	0.532, 2.892	0.618						
La/SSB (current)	2.460	0.823, 7.358	0.107						

[a]In the imputed model, data for hypertension and renal disease were imputed using chained equations (see Methods for more details). [b]There was no change in APS status between pregnancies. Bold text indicates statistically significant results. LMWH: low-molecular-weight heparin. $P < 0.05$ was considered statistically significant.

Table 5 First documented infections during childhood requiring hospital management in 284 children

Infection	Frequency (*n*, %)
Brain abscess	1 (2.08%)
Bronchiolitis	7 (14.58%)
CMV	1 (2.08%)
Chickenpox	1 (2.08%)
Conjunctivitis	1 (2.08%)
Ear infection	1 (2.08%)
Febrile convulsions	4 (8.33%)
Meningitis	3 (6.25%)
Unspecified bacterial infection requiring antibiotics	2 (4.16%)
Pharyngitis or tonsillitis	4 (8.33%)
Pneumonia	11 (22.9%)
Pyrexia of unknown origin (assumed infective)	1 (2.08%)
Urinary tract infection	6 (12.50%)
Unspecified viral infection	3 (6.25%)
Wound infection	2 (4.16%)

which did not identify an increased risk of neurodevelopmental disorders up to mean 14 years of age [32] There was a similar frequency of patients of white and black backgrounds in our study to those above, although we included more patients from Asian backgrounds. There may also be differences in assessment of children by special needs services, notably hearing services, between the USA and UK.

Children with low birth weight were more likely to have been exposed to AZA in utero, although the frequency of babies born <2.5 kg was lower than reported by others [27]. In univariate models, low birth weight was associated with AZA, aspirin and LMWH, but this is likely due to the confounding effect of pre-eclampsia. It is therefore important to adjust for maternal variables in models of early pregnancy outcomes.

Childhood infection requiring hospital management was reported more frequently in children exposed to AZA. As both low birth weight and prematurity are associated with increased childhood infection risk, these were forcibly retained in our models [33]. Similarly, children with a longer period of follow-up may be more likely to have infection, and therefore the follow-up duration was also retained in the multivariable model. Although the foetal liver is unable to convert AZA to 6-mercaptopurine, the active metabolite 6-TGN (but not 6-MMP) is present in both the maternal and foetal circulation and is proposed to contribute to anaemia in children exposed

Table 6 Mixed-effects logistic regression model of infection in children from all pregnancies (n = 283)

	Univariate model			Multivariable model (only variables included in the model are shown)			Imputed multivariable model[a]		
	OR	95% CI	*P*	OR	95% CI	*P*			
Fixed maternal factors									
Ethnic background (white)	**2.445**	**1.107, 5.398**	**0.027**	**2.870**	**0.567, 2.365**	**0.017**	**2.776**	**1.164, 6.620**	**0.021**
History of hypertension	1.759	0.679, 4.560	0.245				1.050	0.293, 3.761	0.940
History of renal disease	1.057	0.467, 2.397	0.898				0.770	0.240, 2.472	0.659
APS[b]	0.539	0.146, 1.992	0.355						
LA	0.944	0.452, 1.972	0.879						
aCL	1.067	0.492, 2.318	0.869						
dsDNA (ever)	1.211	0.534, 2.749	0.646						
Sm (ever)	1.351	0.475, 3.836	0.572						
RNP (ever)	0.842	0.364, 1.947	0.687						
Pregnancy factors									
Maternal age at delivery	1.047	0.979, 1.112	0.180						
Maternal disease duration	0.975	0.906, 1.049	0.501						
Pregnancy number	0.870	0.609, 1.241	0.442						
Birth weight	0.858	0.518, 1.423	0.554	1.158	0.567, 2.365	0.687	1.157	00.568, 2.360	0.688
Low birth weight (<2.5 kg)	1.721	0.815, 3.635	0.154						
Gestational age	0.919	0.812, 1.040	0.180	0.925	0.770, 1.109	0.400	0.922	0.768, 1.106	0.380
Premature delivery (<38 weeks)	1.611	0.746, 3.480	0.224						
Pre-eclampsia	0.566	0.152, 2.101	0.395						
IUGR	1.021	0.322, 3.242	0.971						
Proteinuria	0.831	0.319, 2,160	0.704						
HCQ	0.858	0.423, 1.739	0.671						
AZA	**2.221**	**1.027, 4.804**	**0.043**	**2.283**	**1.003, 5.198**	**0.049**	**2.432**	**1.008, 5.870**	**0.048**
Prednisolone	1.372	0.660, 2.853	0.397	1.217	0.538, 2.753	0.637	1.218	0.539, 2.745	0.636
Aspirin	1.423	0.672, 3.011	0.357						
LMWH	1.418	0.685, 2.936	0.347						
Ro/SSA (current)	0.782	0.385, 1.594	0.500						
La/SSB (current)	1.020	0.433, 2.403	0.964						
Age of child at recruitment/ Follow-up duration (years)[c]	1.024	0.942, 1.112	0.574	1.010	0.929, 1.097	0.822	1.009	0.927, 1.098	0.836

[a]In the imputed model, data for hypertension and renal disease were imputed using chained equations (see methods for more details). [b]There was no change in APS status between pregnancies. [c]Age of recruitment, which defines the follow-up period of the child, was forcibly retained in the model. Bold text indicates statistically significant results. IUGR: intrauterine growth restriction; LMWH: low-molecular-weight heparin; OR: odds ratio. P < 0.05 was considered statistically significant.

to AZA in utero [34]. Other studies, however, suggest that there are no significant differences in lymphocyte count or function due to AZA exposure [35, 36].

A large study of children born to women with IBD receiving AZA with a follow-up of 5 years found no increased risk of infection requiring antibiotics in 240 children [37]. Similarly, a smaller Dutch study of mothers with IBD and follow-up duration similar to our study did not identify increased frequency of severe infection or attendance at primary care in children exposed to AZA in pregnancy/breastfeeding [31]. Our observation may relate to other important unmeasured confounders or increased risk of recall bias over the longer follow-up duration, especially in mothers taking immunosuppressants. Additional unmeasured confounders, including socio-economic factors, may also be important.

It was not possible to study only infections that occurred during breastfeeding although only very low concentrations of 6-MP, and no AZA metabolites, are detected in breast milk [38–40]. In this study, the mother being of a white ethnic group was associated with childhood infection. This could reflect increased childcare usage by this group, which may increase exposure to infection [41]. Alternatively, our study only considered infection requiring secondary care intervention, and fewer outpatient appointment attendances by children from black backgrounds compared with white backgrounds have been reported [42]. Furthermore the number of mothers from non-white backgrounds was small, consistent with known challenges in recruiting women from these backgrounds into research studies.

Strengths of the study

This is the one of the largest studies of outcomes in children born to mothers with SLE extending beyond the

early postnatal period. As women provided data about multiple children, random-effects logistic regression models were used to allow inferences to be made about the exposures and outcome that were not dependent on unmeasured variables related to the mother.

Limitations of the study

Data completed by the mothers are at risk of recall bias, which may be higher in those who continued medication throughout pregnancy. Our study focused on live-born children and is therefore not able to detect any effects of either SLE itself or medication on late pregnancy losses (these events were excluded as there were concerns about the completeness of the data, as some women declined to take part in the study). Information on drug dose was not available precluding examination of dose-dependent relationships. Similarly, changes in drug dosage during pregnancy were not captured. Women receiving AZA were more likely to have a history of renal disease or hypertension, suggesting more severe SLE. Although these factors were adjusted for in the models, there may be therefore other unmeasured confounders related to either the mother or the child contributing to the association between AZA and pregnancy outcomes in this study.

In summary, this large retrospective observational study of pregnancy outcomes in patients with SLE has confirmed that adverse events are relatively rare. HCQ remains a treatment compatible with pregnancy and breastfeeding. AZA was not associated with adverse events in either the mother or foetus. Children who were exposed to AZA during pregnancy/breastfeeding appeared to have a slightly increased risk of infection, but the underlying mechanism is uncertain. We support the view of others [43] that larger prospective pregnancy studies, with lupus patients from diverse racial, ethnic and socio-economic backgrounds, a core minimum dataset and frequent follow-up are required to provide more definitive data that will exclude recall bias and reduce the risk of unmeasured confounders.

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Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author, dependent upon the nature of the request, the availability of the data and its intended use.

Supplementary data

Supplementary data are available at Rheumatology online.

References

1 Clowse MEB. Lupus activity in pregnancy. Rheum Dis Clin North Am 2007;33:237–52, v.

2 Clowse MEB, Magder LS, Witter F, Petri M. Early risk factors for pregnancy loss in lupus. Obstet Gynecol 2006;107:293–9.

3 Eudy AM, Siega-Riz AM, Engel SM et al. Effect of pregnancy on disease flares in patients with systemic lupus erythematosus. Ann Rheum Dis 2018;77:855–60.

4 Clowse ME, Magder L, Witter F, Petri M. Hydroxychloroquine in lupus pregnancy. Arthritis Rheumatol 2006;54:3640–7.

5 Levy RA, Vilela VS, Cataldo MJ et al. Hydroxychloroquine (HCQ) in lupus pregnancy: double-blind and placebo-controlled study. Lupus 2001;10:401–4.

6 Izmirly P, Kim M, Friedman DM et al. Hydroxychloroquine to prevent recurrent congenital heart block in fetuses of anti-SSA/Ro-positive mothers. J Am Coll Cardiol 2020; 76:292–302.

7 Sperber K, Hom C, Chao CP, Shapiro D, Ash J. Systematic review of hydroxychloroquine use in pregnant patients with autoimmune diseases. Pediatr Rheumatol Online J 2009;7:9.

8 Osadchy A, Ratnapalan T, Koren G. Ocular toxicity in children exposed in utero to antimalarial drugs: review of the literature. J Rheumatol 2011;38:2504–8.

9 Flint J, Panchal S, Hurrell A et al.; BSR and BHPR Standards, Guidelines and Audit Working Group. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Rheumatology 2016;55:1693–7.

10 Fischer-Betz R, Specker C, Brinks R, Aringer M, Schneider M. Low risk of renal flares and negative outcomes in women with lupus nephritis conceiving after switching from mycophenolate mofetil to azathioprine. Rheumatology (Oxford) 2013;52:1070–6.

11 Belizna C, Meroni PL, Shoenfeld Y et al. In utero exposure to azathioprine in autoimmune disease. Where do we stand? Autoimmun Rev 2020;19:102525.

12 Gerosa M, Meroni PL, Cimaz R. Safety considerations when prescribing immunosuppression medication to pregnant women. Expert Opin Drug Saf 2014;13: 1591–9.

13 Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40: 1725.

14 Wilson WA, Gharavi AE, Koike T et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. Arthritis Rheum 1999;42: 1309–11.

15 Lechat MF, Dolk H. Registries of congenital anomalies: EUROCAT. Environ Health Perspect 1993;101(Suppl 2): 153–7.

16 Costedoat-Chalumeau N, Georgin-Lavialle S, Amoura Z, Piette JC. Anti-SSA/Ro and anti-SSB/La antibody–mediated congenital heart block. Lupus 2005;14:660–4.

17 Buyon JP, Kim MY, Guerra MM et al. Predictors of pregnancy outcomes in patients with lupus: a cohort study. Ann Intern Med 2015;163:153–63.

18 Andreoli L, Bertsias GK, Agmon-Levin N et al. EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. Ann Rheum Dis 2017;76:476–85.

19 Sammaritano LR, Bermas BL, Chakravarty EE et al. 2020 American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. Arthritis Rheumatol 2020;72: 529–56.

20 Seo MR, Chae J, Kim YM et al. Hydroxychloroquine treatment during pregnancy in lupus patients is associated with lower risk of preeclampsia. Lupus 2019; 28:722–30.

21 Kaplan YC, Ozsarfati J, Nickel C, Koren G. Reproductive outcomes following hydroxychloroquine use for autoimmune diseases: a systematic review and meta-analysis. Br J Clin Pharmacol 2016;81:835–48.

22 Andersson NW, Skov L, Andersen JT. Fetal safety of chloroquine and hydroxychloroquine use during pregnancy: a nationwide cohort study. Rheumatology (Oxford) 2021;60:2317–26.

23 Huybrechts KF, Bateman BT, Zhu Y et al. Hydroxychloroquine early in pregnancy and risk of birth defects. Am J Obstet Gynecol 2021;224:290.e1–e22.

24 Knudsen SS, Simard JF, Knudsen JS et al. Systemic lupus erythematosus during pregnancy is not associated with school performance in offspring – a Danish population-based study. Lupus 2021;30:228–37.

25 Nalli C, Iodice A, Andreoli L et al. Long-term neurodevelopmental outcome of children born to prospectively followed pregnancies of women with systemic lupus erythematosus and/or antiphospholipid syndrome. Lupus 2017;26:552–8.

26 Saavedra M, Sánchez A, Morales S, Ángeles U, Jara LJ. Azathioprine during pregnancy in systemic lupus erythematosus patients is not associated with poor fetal outcome. Clin Rheumatol 2015;34:1211–6.

27 Mahadevan U, Long MD, Kane SV et al.; Crohn's Colitis Foundation Clinical Research Alliance. Pregnancy and neonatal outcomes after fetal exposure to biologics and thiopurines among women with inflammatory bowel disease. Gastroenterology 2021; 160:1131–9.

28 Ban L, Tata LJ, Fiaschi L, Card T. Limited risks of major congenital anomalies in children of mothers with IBD and effects of medications. Gastroenterology 2014;146:76–84.

29 Plauborg AV, Hansen AV, Garne E. Use of azathioprine and corticosteroids during pregnancy and birth outcome in women diagnosed with inflammatory bowel disease. Birth Defects Res A Clin Mol Teratol 2016;106:494–9.

30 Marder W, Ganser MA, Romero V et al. In utero azathioprine exposure and increased utilization of special educational services in children born to mothers with systemic lupus erythematosus. Arthritis Care Res 2013; 65:759–66.

31 de Meij TG, Jharap B, Kneepkens CM, van Bodegraven AA, de Boer NK; Dutch Initiative on Crohn and Colitis. Long-term follow-up of children exposed intrauterine to maternal thiopurine therapy during pregnancy in females with inflammatory bowel disease. Aliment Pharmacol Ther 2013;38:38–43.

32 Lazzaroni MG, Andreoli L, Crisafulli F et al. Neuropsychiatric outcome of children born to women with systemic lupus erythematosus and exposed in utero to azathioprine: a case–control study. Front Pharmacol 2020;11:613239.

33 Miller JE, Hammond GC, Strunk T et al. Association of gestational age and growth measures at birth with infection-related admissions to hospital throughout childhood: a population-based, data-linkage study from Western Australia. Lancet Infect Dis 2016;16:952–61.

34 Jharap B, de Boer NK, Stokkers P et al.; for the Dutch Initiative on Crohn and Colitis. Intrauterine exposure and pharmacology of conventional thiopurine therapy in pregnant patients with inflammatory bowel disease. Gut 2014;63:451–7.

35 Motta M, Ciardelli L, Marconi M et al. Immune system development in infants born to mothers with autoimmune disease, exposed in utero to immunosuppressive agents. Am J Perinatol 2007;24:441–7.

36 Motta M, Tincani A, Meroni PL, Cimaz R. Follow-up of children exposed antenatally to immunosuppressive drugs. Rheumatology 2008;47:iii32–4.

37 Kanis SL, Modderman S, Escher JC et al.; Initiative on Crohns and Colitis (ICC). Health outcomes of 1000 children born to mothers with inflammatory bowel disease in their first 5 years of life. Gut 2021;70: 1266–74.

38 Sau A, Clarke S, Bass J et al. Azathioprine and breastfeeding: is it safe? BJOG 2007;114:498–501.

39 Gardiner SJ, Gearry RB, Roberts RL et al. Exposure to thiopurine drugs through breast milk is low based on metabolite concentrations in mother–infant pairs. Br J Clin Pharmacol 2006;62:453–6.

40 Christensen LA, Dahlerup JF, Nielsen MJ, Fallingborg JF, Schmiegelow K. Azathioprine treatment during lactation. Aliment Pharmacol Ther 2008;28:1209–13.

41 Department of Education. Childcare and Early Years Survey of Parents 2019. Crown Copyright 2019, 2019. https://www.gov.uk/government/statistics/childcare-and-early-years-survey-of-parents-2019 (6 May 2022, date last accessed).

42 Coughlan CH, Ruzangi J, Neale FK et al. Social and ethnic group differences in healthcare use by children aged 0–14 years: a population-based cohort study in England from 2007 to 2017. Arch Dis Child 2022;107:32–9.

43 Vinet E, Chakravarty EF, Clowse MEB. Power in numbers. Rheumatology 2018;57:v40–7.

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JYSELECA® ▽ filgotinib 100 mg or 200 mg film-coated tablets. **Indication:** Jyseleca is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs (DMARDs). Jyseleca may be used as monotherapy or in combination with methotrexate (MTX). **Dosage:** Adults: 200 mg once daily. Taken orally with/without food. It is recommended that tablets are swallowed whole. Laboratory Monitoring: Refer to the SmPC for information regarding laboratory monitoring and dose initiation or interruption. Elderly: A starting dose of 100 mg once daily is recommended for patients aged 75 years and older as clinical experience is limited. Renal impairment: No dose adjustment required in patients with estimated creatinine clearance (CrCl) ≥ 60 mL/min. A dose of 100 mg of filgotinib once daily is recommended for patients with moderate or severe renal impairment (CrCl 15 to < 60 mL/min). Not recommended in patients with CrCl < 15 mL/min. Hepatic impairment: Mild/moderate hepatic impairment: no dose adjustment required. Severe hepatic impairment: not recommended. Children (< 18years): Safety and efficacy not yet established. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Active tuberculosis (TB) or active serious infections. Pregnancy. **Warnings/Precautions:** See SmPC for full information. Immunosuppression: Combination use, with immunosuppressants e.g., ciclosporin, tacrolimus, biologics or other Janus kinase (JAK) inhibitors is not recommended as a risk of additive immunosuppression cannot be excluded. Infections: Infections, including serious infections such as pneumonia and opportunistic infections e.g. tuberculosis (TB), oesophageal candidiasis, and cryptococcosis have been reported. Risk benefit should be assessed prior to initiating in patients with risk factors for infections (see SmPC). Patients should be closely monitored for the development of signs and symptoms of infections during and after filgotinib treatment. Treatment should be interrupted if the patient is not responding to antimicrobial therapy, until infection is controlled. There is a higher incidence of serious infections in the elderly aged 75 years and older, caution should be used when treating this population. Tuberculosis: Patients should be screened for TB before initiating filgotinib, and filgotinib should not be administered to patients with active TB. Viral reactivation: Cases of herpes virus reactivation (e.g., herpes zoster), were reported in clinical studies (see SmPC). If a patient develops herpes zoster, filgotinib treatment should be temporarily interrupted until the episode resolves. Screening for viral hepatitis and monitoring for reactivation should be performed. Malignancy: Immunomodulatory medicinal products may increase the risk of malignancies. Malignancies were observed in clinical studies (see SmPC). Fertility: In animal studies, decreased fertility, impaired spermatogenesis, and histopathological effects on male reproductive organs were observed (see SmPC). The potential effect of filgotinib on sperm production and male fertility in humans is currently unknown. Haematological abnormalities: Do not start therapy, or temporarily stop, if Absolute Neutrophil Count (ANC) <1 × 10^9 cells/L, ALC <0.5 × 10^9 cells/L or haemoglobin <8 g/dL. Temporarily stop therapy if these values are observed during routine patient management. Vaccinations: Use of live vaccines during, or immediately prior to, filgotinib treatment is not recommended. Lipids: Treatment with filgotinib was associated with dose dependent increases in lipid parameters, including total cholesterol, and high-density lipoprotein (HDL) levels, while low density lipoprotein (LDL) levels were slightly increased (see SmPC). Cardiovascular risk: Rheumatoid arthritis patients have an increased risk for cardiovascular disorders. Patients should have risk factors (e.g., hypertension, hyperlipidaemia) managed as part of usual standard of care. Venous thromboembolism: Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving JAK inhibitors including filgotinib. Caution should be used in patients with risk factors for DVT/PE, such as older age, obesity, a medical history of DVT/PE, or patients undergoing surgery, and prolonged immobilisation. Lactose content: Contains lactose; patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take filgotinib. **Pregnancy/Lactation:** Filgotinib is contraindicated in pregnancy. Filgotinib should not be used during breast-feeding. Women of childbearing potential must use effective contraception during and for at least 1 week after cessation of treatment. **Driving/Using machinery:** No or negligible influence, however dizziness has been reported. **Side effects:** See SmPC for full information. Common (≥1/100 to <1/10): nausea, upper respiratory tract infection, urinary tract infection and dizziness. Uncommon (≥1/1000 to <1/100): herpes zoster, pneumonia, neutropenia, hypercholesterolaemia and blood creatine phosphokinase increase. Serious side effects: See SmPC for full information **Legal category:** POM **Pack:** 30 film-coated tablets/bottle **Price:** UK Basic NHS cost: £863.10 **Marketing authorisation number(s):** Great Britain Jyseleca 100mg film-coated tablets PLGB 42147/0001 Jyseleca 200mg film-coated tablets PLGB 42147/0002 Northern Ireland Jyseleca 100mg film-coated tablets EU/1/20/1480/001 EU/1/20/1480/002 Jyseleca 200mg film-coated tablets EU/1/20/1480/003 EU/1/20/1480/004 **Further information:** Galapagos UK, Belmont House, 148 Belmont Road, Uxbridge UB8 1QS, United Kingdom 00800 7878 1345 medicalinfo@glpg.com Jyseleca® is a trademark. **Date of Preparation:** January 2022 UK-RA-FIL-202201-00019

▽ Additional monitoring required

Adverse events should be reported.
For Great Britain and Northern Ireland, reporting forms and information can be found at yellowcard.mhra.gov.uk or via the Yellow Card app (download from the Apple App Store or Google Play Store).
Adverse events should also be reported to Galapagos via email to DrugSafety.UK.Ireland@glpg.com or 00800 7878 1345

References: 1. JYSELECA SPC. Available at: www.medicines.org.uk. Last accessed: June 2022. **2.** Angelini J, *et al.* Biomolecules 2020;10(7):E1002. **3.** Banerjee S, *et al.* Drugs 2017;77:521–546. **4.** O'Shea JJ, *et al.* Nat Rev Rheumatol 2013;9(3):173–182. **5.** Traves PG, *et al.* Ann Rheum Dis 2021;0:1–11. **6.** McInnes IB, *et al.* Arthr Res Ther 2019;21:183. **7.** Combe B, *et al.* Ann Rheum Dis 2021;doi:10.1136/annrheumdis-2020-219214. **8.** Genovese MC, *et al.* JAMA 2019;322 (4):315–325. **9.** Westhovens R, *et al.* Ann Rheum Dis 2021;doi:10.1136/annrheumdis-2020-219213. **10.** Combe B, *et al.* Arthritis Rheumatol 2021;73(suppl 10). https://acrabstracts.org/abstract/clinical-outcomes-up-to-week-48-of-filgotinib-treatment-in-an-ongoing-long-term-extension-trial-of-ra-patients-with-inadequate-response-to-mtx-initially-treated-with-filgotinib-or-adalimumab-during-th/. Last accessed: June 2022. **11.** Buch MH, *et al.* Arthritis Rheumatol 2021;73 (suppl 10). https://acrabstracts.org/abstract/clinical-outcomes-up-to-week-48-of-ongoing-filgotinib-ra-long-term-extension-trial-of-biologic-dmard-inadequate-responders-initially-on-filgotinib-or-placebo-in-a-phase-3-trial/. Last accessed: June 2022. **12.** Winthrop K, *et al.* Arthritis Rheumatol 2021;73(suppl 10). Available at: https://acrabstracts.org/abstract/integrated-safety-analysis-update-for-filgotinib-in-patients-with-moderately-to-severely-active-rheumatoid-arthritis-receiving-treatment-over-a-median-of-2-2-years/. Last accessed: June 2022.

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